

**Remarks**

Claims 28 and 30-46 are currently pending. With this amendment, claims 28 and 30-46 have been cancelled without prejudice, and have been replaced by new claims 47-72. The new claims relate to a non-pathogenic *Bifidobacterium* bacterium comprising particular vectors, and methods of using such bacteria, as did the cancelled claims. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more related applications. The amendment is fully supported by the application as originally filed and, as such, does not constitute new matter. Exemplary support in the specification for new claims 47-72 is summarized in the table below. Applicants request consideration and entry of the remarks into the record. Upon entry of this Amendment, claims 47-72 will be pending.

<b>Claim No.</b>	<b>Support in US 2005/0025745</b>
47	paragraphs [0016]-[0017], [0058]-[0074], [0103], [0113], [0135]
48	paragraph [0115]
49	paragraph [0115]
50	paragraphs [0129]-[0130]; Figures 1 and 6
51	paragraphs [0105]-[0110]
52	paragraph [0105]
53	paragraph [0105]
54	paragraph [0105]
55	paragraph [0105]
56	paragraphs [0125]-[0130], [0134] [235]; Figure 6
57	paragraph [0134], [235]; Examples 2-4
58	paragraph [0074]
59	paragraphs [0074]-[0076]; Examples 2-4
60	paragraphs [0023], [0064]-[0071]
61	paragraphs [0068]-[0071]
62	paragraphs [0068], [0076], [0089], [0125]; Example 3
63	paragraphs [0023], [0064]-[0071], [0076], [0089], [0125]; Example 3
64	paragraphs [0141]-[0144]
65	paragraphs [0002], [0014]-[0016], [0141], [0159]

Claim No.	Support in US 2005/0025745
66	paragraphs [0002], [0014], [0058]-[0071]
67	paragraphs [0023], [0064]-[0071], [0076], [0089], [0125]; Example 3
68	paragraphs [0074]-[0076]
69	paragraph [0069]
70	paragraphs [0074]-[0076]
71	paragraph [0071]
72	paragraphs [0074]-[0076]

**I. The Rejections for Lack of Written Description Should be Withdrawn**

Claims 28 and 30-46 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Patent Office contends that in reading the disclosure of the application, and in particular the working examples, a skilled artisan would not recognize that Applicants were in possession of the claimed subject matter. For at least the following reasons, Applicants respectfully disagree with this rejection.

**A. The Legal Standard**

The test for sufficiency of written description is whether the disclosure of the application “reasonably conveys to the artisan that the inventor had possession” of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); accord *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; see also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement. *See, e.g., In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996) (stating that “[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, *even if [not] every nuance of the claims is explicitly described in the specification*, the adequate written description requirement is met”) (emphasis added).

As reiterated by the Patent Office, the criteria for determining sufficiency of written description are set forth in the Guidelines for Examination of Patent Applications Under 35 U.S.C. 112 ¶ 1, “Written Description Requirement” (“the Guidelines”) (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), which specifies that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).  
*Id.* at p. 1106, column 3, *l.* 13-29.

Furthermore, in accordance with the Guidelines, what is *conventional or well known to one of skill in the art* need not be disclosed in detail (*Id.* at p. 1105, column 3, *ll.* 39-41, emphasis added) and, where the *level of knowledge and skill in the art is high*, a written description question should not be raised. *Id.* at p. 1106, column 1, *ll.* 34-36 (emphasis added). *See also Capon v. Eshhar*, 418 F.3d 1349, at 1357 (Fed. Cir. 2005).

**B. The Claims Comply with the Written Description Requirement**

Claims 28 and 30-46 are no longer pending. Applicants assert, however, that the instant specification provides ample teaching of the claimed subject matter. There is, in fact, no essential critical element of the claimed subject matter that is not described in the specification or conventional in the art.

First, the instant specification discloses multiple species of *Bifidobacterium* that can be routinely used (*see, e.g.*, paragraphs [0072] and [0073]) and systems available for the convenient, routine, and reproducible transformation of the genus *Bifidobacterium*. *See, e.g.*, paragraph [0012], which cites to Argnani, *et al.*, 1996, Microbiology 142:109-14 (“Argnani;” reference AU, of record). Specifically, Argnani describes “the development of a system for efficient and reproducible genetic transformation of strains of the genus *Bifidobacterium*” (Argnani at p. 109,

column 2). Argnani demonstrates the successful transformation of not only *Bifidobacterium longum*, but of multiple species of *Bifidobacterium* (see Table 3 at p. 113 of Argnani).

Second, the specification provides an exemplary listing of known genes encoding proteins having antitumor activity and known genes that encode proteins that convert a precursor of an antitumor substance into an antitumor substance (see, e.g., paragraphs [0061] to [0071]). In addition, at the time the application was filed, methods for identifying, isolating, and testing additional such nucleic acid and protein sequences were standard and well-known in the art.

Third, as acknowledged by the Patent Office, the promoter recited in the pending claims is adequately described. See, p. 4, second full paragraph, of the Office Action mailed on November 26, 2007.

Moreover, while, as explained herein, the instant specification discloses numerous species of the claimed subject matter, Applicants also respectfully point out that compliance with the written description requirement does not require the specific disclosure of every permutation of an invention, but should merely be commensurate with knowledge that comprises the state of the art (see *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005)). In view of *Capon*, the specification's ample disclosure, and the knowledge in the art at the time of filing, Applicants assert that the working example provided *is*, in fact, sufficient to demonstrate to one of skill in the art that Applicants were in possession of the subject matter of the pending claims at the time of filing.

Finally, Applicants respectfully point out that the Patent Office's attempt to apply the holding of *Fiddes v. Baird*, 30 USPQ2d 1481, (1993) to the currently claimed subject matter is inappropriate. In *Fiddes*, the claims of the Baird patent were broadly directed to mammalian fibroblast growth factors (FGF) yet only bovine pituitary FGF was taught in the Baird patent. Because the structure of only one species (bovine pituitary FGF) of the genus existed at the time of Baird's filing, it was held that Baird's broad claims to the genus of mammalian FGFs were unpatentable. In contrast, as pointed out above, the instant specification teaches numerous species of the claimed genus of subject matter. In particular, the instant specification discloses numerous species of *Bifidobacterium* and methods by which said species can be transformed, numerous antitumor substances as well as multiple combinations of proteins that convert a precursor of an antitumor substance into an antitumor substance and antitumor substance

precursors, and a particularly recited promoter, the HU promoter. As such, in contrast to the facts of *Fiddes*, the instant specification's disclosure clearly describes numerous species of the claimed genus.

For at least the foregoing reasons, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of written description, be withdrawn.

## **II. The Rejections for Obviousness Should be Withdrawn**

Claims 28 and 30-46 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Yazawa, *et al.* (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999; "Yazawa") in view of Brown, *et al.* (US. Publication NO. 2003/0103952; "Brown"), and in further view of both Goshima, *et al.* (Biochimie, Vol. 72, pp. 207-214, 1990; "Goshima") and Natori, *et al.* (Biochimie, Vol. 70:12, pp. 1765-1774, 1988; "Natori"). Without acquiescing to the propriety of the rejection, claims 28 and 30-46 have been cancelled. Applicants assert, however, that the currently pending claims are not obvious in view of the cited references.

### **A. The Legal Standard**

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a).

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467. Moreover, the *KSR* Court provides some guidance regarding when a particular combination of elements that may be "obvious to try" can be legally obvious under § 103(a). Further, the relevant inquiry is whether the prior art suggests the

invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

In making a determination of obviousness, one must consider the prior art from the perspective of a person having ordinary skill in the art at the time the invention was made. “Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). The KSR Court, citing *Graham*, upheld the principle of avoiding hindsight bias and cautioned courts to guard against reading into the prior art the teachings of the invention in issue. 127 S.Ct. at 1742, 82 USPQ at 1397:

A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into the use of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

**B. Yazawa, Either Alone or Combined with Brown, Goshima, or Natori Fails to Teach or Suggest the Claimed Invention**

The Patent Office alleges that it would have been obvious to modify the teaching of Yazawa with that of Brown and Natori or Goshima to generate genetically modified *B. longum* comprising DNA that encodes a protein capable of converting a precursor of an anti-tumor substance into the anti-tumor substance, and to include the HU promoter as a means to highly express the anti-tumor substance.

The Patent Office acknowledges that neither Yazawa nor Brown disclose a *Bifidobacterium* HU promoter, and cites Natori and Goshima to contend that this promoter was in the art at the time the application was filed. Applicants assert, however, that contrary to the Patent Office’s contention, neither Natori nor Goshima disclose a *Bifidobacterium* HU promoter. Natori merely discusses the characterization and promoter selectivity of *Lactobacillus acidophilus* RNA polymerase. Nowhere, however, does Natori disclose or contemplate a *Bifidobacterium* HU promoter or a HU promoter from any other bacterium. Goshima allegedly

identifies the existence and purification of a HU-like protein in *B. longum*, but fails to provide any disclosure whatsoever of the regulatory sequence, *e.g.*, the promoter, that might regulate the nucleic acid sequence encoding the HU-like protein. Moreover, in view of the fact that the *Bifidobacterium* HU promoter had *not* been characterized at the time the application was first filed, one of ordinary skill would have had no way of knowing how the promoter would act. Thus, even if a person of ordinary skill in the art were to attempt to modify the disclosure of Yazawa taken with Brown with Natori and/or Goshima, in view of the state of the art at the time the application was filed, they would fail to yield the claimed subject matter, and certainly would not have been provided with a reasonable expectation of success.

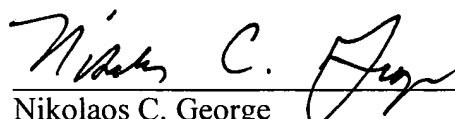
For at least the foregoing reasons, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a), for obviousness, be withdrawn.

**Conclusion**

The Applicants respectfully request entry and consideration of the foregoing amendments and remarks. No new matter has been introduced. The claims are believed to be free of the art and patentable. Withdrawal of all the rejections and an allowance are earnestly sought.

Respectfully submitted,

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Enclosure